poisoning of said bacteria by said fluoroacetamide indicates said test compound has antivirulence activity against *Pseudomonas* bacteria.

Please cancel claim 4 without prejudice or disclaimer.

Remarks

Applicants appreciate the thorough examination of the present application as evidenced by the Office Action dated March 11, 2003 (the Action). Additionally, Applicants appreciate the opportunity provided to the Applicants' representatives, Shawna Cannon Lemon and Kenneth D. Sibley, to conduct a telephonic interview with the Examiner on May 14, 2003 to discuss this case.

Claims 1-9 are pending in the present application. Applicants have submitted a replacement Abstract of the Disclosure pursuant to suggestions presented by the Examiner. Applicants have cancelled claim 4 for the purpose of incorporating the subject matter of dependent claim 4 into independent claim 1. Such amendments relate to form only, and do not pertain to issues relative to the prior art, and are fully supported by the application as originally filed.

Claims 1-9 stand rejected under 35 U.S.C. § 112, second paragraph, 35 U.S.C. § 112, first paragraph, and 35 U.S.C. § 103. The concerns raised by the Examiner are addressed below as set forth in the Action.

I. Specification

Applicants have submitted a replacement Abstract of the Disclosure pursuant to the Examiner's suggestions. The replacement Abstract of the Disclosure is in narrative form composed of clear and concise language.

Accordingly, Applicants respectfully request that the objection to the Abstract of the Disclosure be withdrawn.

II. Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

Claim 8 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite with respect to the recitation "combinatorial library." More specifically, the Examiner states that "the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Clarification is required." Action, page 3. Applicants respectfully traverse this rejection.

In contrast to the assertion that "combinatorial library" is a relative term (*see* Action, page 3), Applicants respectfully submit that "combinatorial library", as used herein and as known to one of ordinary skill in the art, refers to a plurality of compounds produced by combining chemical or biochemical building blocks and may comprise pools or sub-libraries. Moreover, as noted in the specification, the combinatorial libraries of the present invention are, in general, small organic compounds, oligomers, or combinations thereof. Non-limiting examples of small organic molecules are listed in the specification on page 5, lines 1-5. Non-limiting examples of libraries of such compounds are listed in the specification on page 5, lines 5-9. Non-limiting examples of oligomers are also listed in the specification on page 5, lines 10-16. Further, on page 5, lines 16-22, it is noted in the specification that such oligomers may be obtained from, among other sources, combinatorial libraries in accordance with known techniques. In view of the use of "combinatorial library" consistent with its meaning as understood by those of ordinary skill in the art combined with the description provided in the specification, Applicants respectfully submit that one of ordinary skill in the art would be reasonably apprised of the scope of the present invention.

Accordingly, Applicants respectfully submit that claim 8 is not indefinite under 35 U.S.C. § 112, second paragraph and request that this rejection be withdrawn.

III. Claim Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1-9 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking written description.

Applicants acknowledge with appreciation the telephone interview provided by Examiner Gibbs and her Supervisor Ram Shukla with Ms. Lemon and Mr. Sibley on May 14,

2003. During the interview, the written description rejection of record was discussed. It was pointed out that the claims of record were directed to methods of screening compounds, and not to compounds *per se* or to methods of using such compounds. It was submitted that for claims to such screening methods an application of the written description requirement to the compounds to be screened was inappropriate as, if such compounds could be described, there would be no need for the screening technique. The Examiners indicated agreement with this line of reasoning and indicated that the written description rejection of Claims 1-9 would be dropped. This action is respectfully requested. Applicants' representatives indicated that they would then proceed to address the remaining Section 103 rejection on the record, which is done so below.

IV. Claim Rejections Under 35 U.S.C. § 103

Claims 1-9 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Bright et al., Abstract, 96th ASM General Meeting, pp. 220 (1996) (Bright et al. (a)), Bright et al., Abstract, Cystic Fibrosis Conference, pp. 225 (1995) (Bright et al. (b)), and further in view of U.S. Patent Application Serial No. 09/927885 to Mahan et al. (Mahan et al.), MacGregor et al., Journal of Bacteriology, pp. 5627-5635 (1996) (MacGregor et al.), O'Toole et al, Journal of Bacteriology, pp. 425-431 (2000) (O'Toole et al.), and WO Patent No. 98/03533 to Arrow et al. (Arrow et al.). More specifically, the Action states the following:

> One of ordinary skill in the art would have been motivated to include the Crc locus because this gene is involved in the regulation of multiple catabolic pathways and **may be important** in the adaptive response of the organism to the milieu within the lung (see Bright et al. (b)).

Action, page 7 (emphasis added). Applicants respectfully traverse this rejection.

Applicants maintain the reasons set forth in the Amendment dated December 18, 2002 (Paper No. 10) responsive to the Office Action dated July 18, 2002 in support of the assertion that the Patent Office has failed to establish a *prima facie* case of obviousness under 35 U.S.C. § 103. Applicants have also amended claim 1 to recite as follows:

> A method of screening for compounds that inhibit the virulence of *Pseudomonas* bacteria, comprising the steps of:
>
> providing a culture medium comprising *Pseudomonas* bacteria **and an amidase operon repressor, wherein the culture medium contains fluoroacetamide in an amount toxic to said bacteria in the absence of said amidase operon repressor**;
>
> administering a test compound to said bacteria; and then
>
> **detecting the poisoning of said bacteria by said fluoroacetamide, wherein the poisoning of said bacteria by said fluoroacetamide indicates said test compound has antivirulence activity against *Pseudomonas* bacteria** (emphasis added).

Thus, Applicants respectfully submit that contrary to the assertions of the Action, one of ordinary skill in the art would not be motivated to modify or combine the cited references to arrive at the present invention.

Applicants note that none of the **six** references teach or suggest a method of screening for compounds that inhibit the virulence of *Pseudomonas* bacteria comprising, among other things, the steps of providing a culture medium comprising *Pseudomonas* bacteria and an amidase operon repressor, wherein the culture medium contains fluoroacetamide in an amount toxic to said bacteria in the absence of said amidase operon repressor and detecting the poisoning of said bacteria by said fluoroacetamide, wherein the poisoning of said bacteria by said fluoroacetamide indicates said test compound has antivirulence activity against *Pseudomonas* bacteria as recited in claim 1. It is only in view of the disclosure of the present application that one of ordinary skill in the art is provided an enabling disclosure by which to arrive at the present invention. For none of the cited references show a correlation between virulence and the Crc protein in an animal model. Bright et al. (a) and (b) merely suggest that the crc gene "may be important in the adaptive response of the organism to the milieu within the lung" as previously stated above. In contrast, Example 1 of the present application discloses the virulence of *crc+* and *crc-* employing the *Pseudomonas aeruginosa* in a mouse burn model. This study shows that the assay of the present invention as recited in claim 1 is useful in inhibiting Crc function and shows a correlation to an increase in survival rate.

With respect to the other cited references, as noted in the Office Action dated July 18, 2002, Mahan et al., does not teach detecting the presence or absence of inhibition of the

catabolite repression control protein in an inhibitor of virulence assay. *See* Office Action dated July 18, 2002, page 6. Moreover, MacGregor et al. merely proposes cloning and sequencing of the *crc* gene. *See* abstract. O'Toole et al. merely proposes a role of Crc in the signal transduction pathway that regulates biofilm development by *Pseudomonas aeruginosa*. *See* abstract. Lastly, Arrow et al. generally relates to antisense oligonucleotides that target mRNAs in cells as substrates for the cellular enzyme RNase H. *See* abstract. These additional references do not supply the missing recitations to enable one of ordinary skill in the art to arrive at the present invention. Clearly, it is only in view of the present invention providing, among other things, animal data in the form of the mouse burn model that one of ordinary skill in the art is able to arrive at the present invention directed to a method for screening for compounds that inhibit the virulence of *Pseudomonas* bacteria comprising, among other things, the steps of providing a culture medium comprising *Pseudomonas* bacteria and an amidase operon repressor, wherein the culture medium contains fluoroacetamide in an amount toxic to said bacteria in the absence of said amidase operon repressor and detecting the poisoning of said bacteria by said fluoroacetamide, wherein the poisoning of said bacteria by said fluoroacetamide indicates said test compound has antivirulence activity against *Pseudomonas* bacteria as recited in claim 1.

Accordingly, Applicants respectfully submit that claim 1, and claims that depend therefrom, are not unpatentable under 35 U.S.C. § 103(a) in view of Bright et al. (a), Bright et al. (b), Mahan et al., MacGregor et al., O'Toole et al., and Arrow et al. and request that this rejection be withdrawn.

IV. Conclusion

In view of the foregoing remarks, Applicants respectfully request that all outstanding rejections to the claims be withdrawn and that a Notice of Allowance be issued in due course. Any questions that the Examiner may have should be directed to the undersigned, who may be reached at (919) 854-1400.

Respectfully submitted,

Shawna Cannon Lemon
Registration No. 53, 888

20792
PATENT TRADEMARK OFFICE

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Alexandria, Virginia 22313-1450, on June 11, 2003.

Vickie Diane Prior
Date of Signature: June 11, 2003

Version with Markings to Show Changes Made

1. (Amended) A method of screening for compounds that inhibit the virulence of *Pseudomonas* bacteria, comprising the steps of:

providing a culture medium comprising *Pseudomonas* bacteria and an amidase operon repressor, wherein the culture medium contains fluoroacetamide in an amount toxic to said bacteria in the absence of said amidase operon repressor;

administering a test compound to said bacteria; and then

detecting the **[presence or absence of inhibition of the catabolite repression control (Crc) protein in said bacteria, the inhibition of the Crc protein indicating said compound has antivirulence activity against *Pseudomonas* bacteria]** poisoning of said bacteria by said fluoroacetamide, wherein the poisoning of said bacteria by said fluoroacetamide indicates said test compound has antivirulence activity against *Pseudomonas* bacteria.